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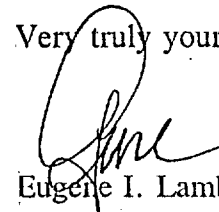
Dr. G. A. Mitchell  
Associate Director  
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Dear Bert:

As promised, I am enclosing a copy of the C&B memo that reviews the recently-enacted FDA reform legislation from the specific viewpoint of veterinary drugs. In addition to providing a general background on the legislation, it reviews provisions that specifically affect animal drugs, or that generally pull animal drugs within their scope (e.g., the National Uniformity provision).

As you know, most of the legislation focused on human drugs, biologics and devices as well as a significant element dealing with human foods. We have done overview memoranda on these areas as well and can provide them if you think anyone in the Center would be interested.

Very truly yours,



Eugene I. Lambert

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Enclosure

97N-0217

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November 12, 1997

## **FDA REFORM LEGISLATION**

### **Its Effect on Animal Drugs**

A number of the provisions of the Food and Drug Administration Modernization Act of 1997 ("the 1997 Act") directly affect or benefit manufacturers of new animal drugs. Some of the improvements contained in this legislation supplement those made by the Animal Drug Availability Act of 1996 ("ADAA"). This memo covers those provisions that specifically affect animal drug manufacturers.

### **I. Background**

Since the enactment of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") in 1938,<sup>1</sup> the statute has been amended more than a hundred times to add, revise, and delete regulatory requirements. One attempt to recodify the entire FD&C Act failed in the early 1950s<sup>2</sup> and has not been attempted since. No legislation has attempted to achieve reform in all aspects of FDA's regulatory jurisdiction. Comprehensive approaches to reform drug regulation in the late 1970s<sup>3</sup> and food regulation in the early 1980s<sup>4</sup> were unsuccessful. All reform has therefore come in the form of narrowly targeted statutes and by FDA administrative action.

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<sup>1</sup> 52 Stat. 1040 (1938), 21 U.S.C. 301 et seq.

<sup>2</sup> H.R. Rep. No. 906, 84th Cong., 1st Sess. (1955).

<sup>3</sup> The Drug Regulation Reform Acts of 1978 and 1979, S. Rep. No. 96-321, 96th Cong., 1st Sess. (1979).

<sup>4</sup> The Food Safety Amendments of 1971, 127 Cong. Rec. 13969 (June 25, 1981).

Following the congressional elections of November 1994, the new Republican majority reached consensus that comprehensive FDA reform would be a major priority. Numerous hearings were conducted in both the House and the Senate. Legislation was introduced in the Senate in December 1995<sup>5</sup> and was reported out of committee in March 1996.<sup>6</sup> Three parallel House bills were introduced in March 1996 (one each for drugs (including biological products),<sup>7</sup> food,<sup>8</sup> and devices<sup>9</sup>) and were the subject of hearings but were not reported out of committee. Because 1996 was a presidential election year, there was simply not enough time for Congress to complete action on what was unquestionably comprehensive legislation. Only consensus reform in animal drug regulation was enacted.<sup>10</sup>

Following the November 1996 elections, Congress returned to this issue. This time, however, there was a new dimension and a greater urgency to the matter. Congress had enacted the Prescription Drug User Fee Act (PDUFA) in 1992,<sup>11</sup> with a five-year life that expired at the end of September 1997. The congressional leadership concluded that the

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<sup>5</sup> S. 1477, 104th Cong., 1st Sess. (1995).

<sup>6</sup> S. Rep. No. 104-284, 104th Cong., 2d Sess. (1996).

<sup>7</sup> H.R. 3199, 104th Cong., 2d Sess. (1996).

<sup>8</sup> H.R. 3200, 104th Cong., 2d Sess. (1996).

<sup>9</sup> H.R. 3201, 104th Cong., 2d Sess. (1996).

<sup>10</sup> Animal Drug Availability Act of 1996, 110 Stat. 3151 (1996), principally codified in 21 U.S.C. 354, 360b, sections 504 and 512 of the FD&C Act.

<sup>11</sup> 106 Stat. 4491 (1992), 21 U.S.C. 379g, section 735 of the FD&C Act.

FDA reform legislation considered in 1996 would be tied to reenactment of PDUFA for another five years.

FDA reform legislation was introduced in the Senate in June 1997,<sup>12</sup> was reported out of committee a month later,<sup>13</sup> was debated on the floor of the Senate beginning on September 5,<sup>14</sup> and was passed by a vote of 98-2 on September 24.<sup>15</sup> Bills were introduced in the House for drugs (including biological products) in April,<sup>16</sup> for medical devices in May,<sup>17</sup> and for food in September.<sup>18</sup> All three bills were reported out of committee in October, with separate reports for each.<sup>19</sup> The three bills were combined and passed by the House without debate under a suspension of the rules on October 7.<sup>20</sup>

As passed by the Senate and the House, both the form of the FDA reform legislation and many of the specific provisions were substantially different. These differences were reconciled during meetings that extended throughout October and into November. After

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<sup>12</sup> S. 830, 105th Cong., 1st Sess. (1997).

<sup>13</sup> S. Rep. No. 105-43, 105th Cong., 1st Sess. (1997).

<sup>14</sup> 143 Cong. Rec. S8837 (September 5, 1997) (daily ed.).

<sup>15</sup> 143 Cong. Rec. S9811-S9868 (September 24, 1997) (daily ed.).

<sup>16</sup> H.R. 1411, 105th Cong., 1st Sess. (1997).

<sup>17</sup> H.R. 1710, 105th Cong., 1st Sess. (1997).

<sup>18</sup> H.R. 2469, 105th Cong., 1st Sess. (1997).

<sup>19</sup> H.R. Rep. No. 105-306 (food), H.R. Rep. No. 105-307 (devices), and H.R. Rep. No. 105-310 (drugs), 105th Cong., 1st Sess. (1997).

<sup>20</sup> 106 Stat. 4491 (1992), 21 U.S.C. 379g, section 735 of the FD&C Act.

marathon sessions in early November, the Conference Committee completed its work and issued its report and the legislation was passed by both Houses of Congress on Sunday, November 9, shortly before the end of the session. The final legislation largely took the form of the bill passed by the House on September 24, and included most of the provisions that were included in the House bill but not in the Senate bill. Viewed as a whole, the 1997 Act represents a major change in the existing law. It includes extremely important statutory amendments throughout the FD&C Act that will require major change in current FDA policy and practice. It is therefore of vital importance to the entire regulated industry.

## **II. Reform Provisions Affecting Animal Drugs**

### **1. Supplemental Applications - Sec. 403.**

FDA is directed, within 180 days of enactment, to publish performance standards for the prompt review of supplemental applications for approved drugs. The Center for Veterinary Medicine (comparably to CDER and CBER) will be responsible for identifying an individual whose role it will be to encourage the prompt review of supplemental applications. In particular, FDA is supposed to work with sponsors and professional, medical, and scientific societies to identify published and unpublished research that can support supplemental applications for new uses. This new requirement will also push FDA to consider whether an improved supplemental policy will be responsive to the requirement

in the ADAA<sup>21</sup> that FDA consider regulatory options to facilitate approvals for uses in minor species and for minor uses.

## **2. Manufacturing Changes - Sec. 116.**

The legislation adds a new section 506A to the FD&C Act that establishes for all types of drugs that FDA approves -- human drugs, animal drugs and animal biologics -- the criteria under which FDA can require either preapproval or pre-use notification of changes in manufacturing practices following initial approval of the drug. In every case, however, the applicant must validate the effects of the change on the identity, strength, quality, purity and potency of the drug, as those attributes may affect safety and efficacy.<sup>22</sup>

The legislation, in part, codifying actions already taken by CVM and other drug centers, requires that the agency distinguish between major and minor manufacturing changes, and sets up three different systems for handling these changes.

"Major changes" continue to require FDA pre-approval, and are generally defined as those that have a "substantial potential" to adversely affect the quality, safety, or effectiveness of the drug.<sup>23</sup>

With respect to other changes, FDA is required to distinguish again between those changes for which a supplemental application must be submitted and those changes for

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<sup>21</sup> Section 2(f), 110 Stat. at 3154.

<sup>22</sup> Section 506A(b) of the FD&C Act.

<sup>23</sup> Section 506A(c) of the FD&C Act.

which some periodic report may be submitted.<sup>24</sup> In the case of changes requiring the submission of a supplement, sponsors are authorized to commence using the changes if FDA does not, within 30 days of submitting the supplemental application, notify the sponsor that approval is required prior to instituting the change.<sup>25</sup> FDA is also authorized (1) to identify those changes covered by a supplement that are permitted to be made immediately effective<sup>26</sup> and (2) to permit manufacturing changes that are subject to reporting to be compiled on an annual basis.<sup>27</sup> CVM has been permitting biennial reporting, and the approved language is sufficiently flexible to permit the continuation of that practice.

To the extent that the legislation alters current practices, it does not become effective until FDA adopts implementing regulations, or after 24 months of enactment if such regulations have not been adopted.<sup>28</sup>

### **3. Dispute Resolution - Sec. 404.**

The industry draft of the Animal Drug Availability Act contained a provision for resolving scientific disputes during the new animal drug review process; that provision was dropped during development of the consensus legislation.

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<sup>24</sup> Section 506A(d)(1)(C) of the FD&C Act.

<sup>25</sup> Section 506A(d)(3)(B)(i) of the FD&C Act.

<sup>26</sup> Section 506A(d)(3)(B)(ii) of the FD&C Act.

<sup>27</sup> Section 506A(d)(2)(B) of the FD&C Act.

<sup>28</sup> 1997 Act, §116(b).

The 1997 Act adds a new section 562, "Dispute Resolution," to the FD&C Act that is applicable to human drugs, animal drugs, and animal biologics. FDA is required, within one year of enactment, to publish regulations providing a mechanism for resolving scientific disputes. That mechanism can include the use of a new scientific advisory panel system established for new drugs<sup>29</sup>, or the use of medical device advisory committees. In the case of animal drugs, FDA could either use the new scientific panels, or could use the existing Veterinary Medicine Advisory Committee, or could establish a wholly separate procedure.

**4. Guidance Documents - Sec. 405.**

FDA has over the years issued a variety of guidance documents relating to compliance with submission requirements, using titles such as "Guideline," "Points to Remember," and "Technical Assistance Documents." The 1997 Act amends Section 701 of the FD&C Act, which contains both the general rulemaking authority<sup>30</sup> and the unique rulemaking by trial provisions<sup>31</sup> by adding a new subsection (h) directing FDA to establish guidance documents "with public participation".<sup>32</sup> As is currently the case, these guidance documents would not create or confer any rights on applicants and would not bind FDA, although FDA employees should "not deviate from such guidelines without appropriate

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<sup>29</sup> 1997 Act, §120, adding 21 U.S.C. 355(n), section 505(n) of the FD&C Act.

<sup>30</sup> Section 701(a) of the FD&C Act, 21 U.S.C. 371(a).

<sup>31</sup> Sections 701(e)-(f) of the FD&C Act, 21 U.S.C. 371(e)-(f).

<sup>32</sup> Section 701(h)(1)(A) of the FD&C Act, 21 U.S.C. 371(h)(1)(A).

justification and supervisory concurrence."<sup>33</sup> The new statutory provision in effect codifies the criteria adopted by FDA in February 1997<sup>34</sup> called "Good Guidance Practices." FDA is directed not later than July 1, 2000, after evaluating the GGP's in practice, to issue regulations implementing the statutory criteria for the development, issuance, and use of guidance documents.<sup>35</sup>

#### **5. Scale-Up Manufacturing - Sec. 124.**

The 1997 Act adds a new provision to Section 512 concerning new animal drug applications,<sup>36</sup> permitting an applicant to rely on drugs manufactured in a pilot or other small scale manufacturing facility to be used in tests for safety and effectiveness, and to obtain approval based on those studies prior to scaling up for commercial manufacturing, unless FDA makes an affirmative determination that product from a full scale production facility "is necessary to ensure" safety or effectiveness. The Senate Report characterizes this need as "very rare" and points out that post-approval scale-up changes will be covered by the new statutory provisions dealing with manufacturing changes (item 2 above) that may facilitate that process as well.<sup>37</sup>

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<sup>33</sup> Section 701(h)(1)(B) of the FD&C Act, 21 U.S.C. 371(h)(1)(B).

<sup>34</sup> 62 Fed. Reg. 8961 (1997).

<sup>35</sup> Section 701(h)(5) of the FD&C Act, 21 U.S.C. 371(h)(5).

<sup>36</sup> Section 512(c)(4) of the FD&C Act, 21 U.S.C. 360b(c)(4).

<sup>37</sup> S. Rep. No. 105-43, 105th Cong., 1st Sess., 38 (July 1, 1997).

## 6. Environmental Impact Review - Sec. 411.

FDA has recently revised its environmental regulations to provide numerous categorical exclusions from the preparation of an environmental assessment, although more new animal drugs are still covered than human drugs.<sup>38</sup> The new legislation adds a new Section 746 to the Act that has the effect of codifying into law the FDA regulations as in effect on August 31, 1997.

## 7. National Uniformity - Sec. 412.

A new national uniformity provision, Section 751 of the FD&C Act, covers both the labeling and safety and efficacy evaluation of animal drugs that are not subject to section 503(f) of the FD&C Act.<sup>39</sup> Thus, all animal drugs added to animal feed (including Veterinary Feed Directive drugs),<sup>40</sup> and all dosage form and drinking water products that are not limited to use by or on the order of a veterinarian are now subject solely to Federal requirements; no state or locality may add a requirement different from or in addition to, i.e., not identical with Federal requirements under the Federal Food, Drug, and Cosmetic Act, the Fair Packaging and Labeling Act, and the Poison Prevention Packaging Act. States may apply to FDA for exemption from national uniformity based on "important public interest[s]" that would otherwise be unprotected where the state requirement would not cause the drug to violate Federal law and the requirement would not unduly burden interstate

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<sup>38</sup> 21 C.F.R. Part 25.

<sup>39</sup> 21 U.S.C. 353(f).

<sup>40</sup> Section 504 of the FD&C Act, 21 U.S.C. 354.

commerce.<sup>41</sup> However, requirements under California Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act) and state product liability law are excluded from, the scope of national uniformity,<sup>42</sup> as are actions with respect to misleading advertising under state "Little FTC Acts".<sup>43</sup> The legislation expands the scope of factory inspection and establishes new labeling requirements for human OTC drugs<sup>44</sup>; none of these changes apply to animal drugs.

**8. Registration of Foreign Establishments - Sec. 417.**

The legislation amends Section 510(i) of the Act that previously had required only drug listing by foreign establishments to require both registration and listing.<sup>45</sup> This new requirement would apply to any establishment exporting drugs solely for animal use to the United States. FDA is also directed to enter into cooperative arrangements with foreign governments to help assure that foreign establishments comply with current good manufacturing requirements. This provision takes effect 90 days after enactment.<sup>46</sup>

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<sup>41</sup> Section 751(b)(1) of the FD&C Act.

<sup>42</sup> Sections 751(d)(2),(e) of the FD&C Act.

<sup>43</sup> Joint Explanatory Statement of the Committee on Conference on S.830, pp. 13-14.

<sup>44</sup> 1997 Act, §412(b)-(c), amending sections 502(e)(1) and 704(a)(1) of the FD&C Act, 21 U.S.C. 352(e)(1), 374(a)(1).

<sup>45</sup> 21 U.S.C. 360(i).

<sup>46</sup> 1997 Act, §501.

**10. Interstate Commerce - Sec. 419.**

Section 709 of the Act, which currently creates a presumption that devices are in interstate commerce, is amended to provide that the requisite interstate commerce connection for FDA jurisdiction is presumed to exist for all articles subject to the Act, including animal drugs.<sup>47</sup> Thus, as a practical matter, FDA will no longer have to document interstate commerce in order to obtain regulatory jurisdiction, or court jurisdiction, over violative products.

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The "reforms" with respect to manufacturing changes and scale up production, as well as the provisions dealing with scientific dispute resolution, are useful complements to the improvements made by the ADAA. The environmental and guidance practice provisions essentially codify current FDA practices rather than provide additional relief or reform. Most of these provisions, like those in the ADAA, require FDA implementation, so that the scope of any actual benefit will be dependent on the actual regulatory implementation, which varies from 6 months to 2 years after enactment.

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<sup>47</sup> 21 U.S.C. 379a.